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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/624,447	07/21/2003	Tod Woolf	089596-0502	3208

30542 7590 12/06/2006

FOLEY & LARDNER LLP
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER

ZARA, JANE J

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 12/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/624,447

Applicant(s)

WOOLF, TOD

Examiner

Jane Zara

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>10-24-03, 8-4-05, 10-24-03</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office action is in response to the communication filed 9-28-06.

Claims 1-18 are pending in the instant application.

Election/Restrictions

The restriction requirement mailed 3-28-06 is hereby vacated and claims 1-18 have been examined on their merits as set forth below.

Claim Objections

Claim 16 is objected to because it appears to be grammatically incorrect (e.g., inserting the verb —is— before “linked” in line 2 would be remedial).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

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not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arrow et al. and Srivastava et al., the combination further in view of Baracchini et al. and in view of Gryaznov et al. and Friesen et al.

The claims are drawn to methods of inhibiting target gene expression in vitro comprising the administration of chimeric oligonucleotides comprising an RNase activating region, an RNase non-activating region, a nucleomonomer modified to contain a 2'-O-propargyl group with respect to its sugar, modified internucleotide linkages, including P-alkyloxyphosphotriester and phosphorothioate containing linkages, inverted nucleomonomers, biotin, regions of nucleotide gaps within the chimera which contain variously modified nucleotides occupying different regions of the chimeric construct and relative to the 5' and 3' termini, and relative to the other components within the chimeric construct.

Arrow et al (5,849,902) teach methods of inhibition of target gene expression in vitro comprising the administration of oligonucleotides which target a specific RNA for RNase H degradation, which oligonucleotides contain nuclease resistant bases, including the incorporation of 2'-O-modifications into oligonucleotides for enhancing stability. Arrow teaches an RNase non-activating region within the oligonucleotide and the presence of modified nucleotides within the RNase activating region, as well as modifications within the RNase non-activating region, which oligonucleotides are

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optimally between 15-50 nucleotides (col. 3-col. 4). Arrow also teaches the significance of the location of the RNase activating region within the antisense construct on the oligonucleotide's stability (col. 8, line 14-col. 9, line 17; tables II and III).

Srivastava et al (USPN 5,744,595) teach the incorporation of 2'-O-propargyl modifications into oligonucleotides for increasing oligonucleotide stability (col. 3, line 66-col. 4, line 3).

Baracchini et al (USPN 5,801,154) teach the inhibition of target gene expression in vitro comprising the administration of oligonucleotides that specifically target a gene of known sequence, which oligonucleotides comprise sugar, base and internucleotide modifications for enhancing target binding, cellular uptake and oligonucleotide stability, including phosphorothioate and 2'-alkoxy linkages, chimeric oligonucleotides and regions of gapped oligonucleotides within the chimera (col. 6-8).

The primary references of Arrow, Srivastava and Baracchini do not teach biotin as a reporter moiety for diagnostic tools, nor 3'-3' and 5'-5' inversions.

Gryaznov et al (USPN 5,965,720) teach the use of reporter moieties on oligonucleotides, including biotin for use as a diagnostic tool (col. 4).

Friesen (USPN 5,594,122) teaches the use of compositions containing parallel stranded nucleic acids, including 3'-3' and 5'-5' inversions (col. 3), which render the termini resistant to exonuclease degradation..

It would have been obvious to one of ordinary skill in the art to modify the oligonucleotides taught by Arrow which contain RNase activating as well as RNase non-activating regions with the prior art sugar modifications for 2'-O-propargyl taught by

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Srivastava and use these oligonucleotides in methods of inhibiting target gene expression in vitro. One of ordinary skill in the art would have been motivated to utilize the 2'-O-propargyl modifications within the RNase non-activating region of the oligonucleotides taught by Arrow because Arrow teaches utilizing modified nucleotides in this region, including the incorporation of 2'-O-modification, for enhancing oligonucleotide stability. One of ordinary skill in the art would have been motivated to utilize 2'-O-propargyl modification because these were previously taught by Srivastava to increase oligonucleotide stability and such modifications would have provided the benefits outlined by Srivastava et al. Such benefits would be applicable in any nucleotide, including that described by Arrow. A person of ordinary skill in the art would have been motivated to include these features claimed for enhancing stability and hence enhancing effectiveness of oligonucleotides in targeting and inhibiting the expression of a target gene. One of ordinary skill would have expected that the incorporation of 2'-O-propargyl groups would enhance oligonucleotide stability in a manner previously taught by Srivastava. Unmodified residues and unmodified internucleotide linkages in such structures are historically considered inherent properties of oligonucleotides.

It would have been obvious to one of ordinary skill in the art to design and construct the chimeric oligonucleotides claimed for methods of inhibiting the expression of a known target gene, including the inclusion of modified internucleotide linkages, sugar modifications, inverted nucleomonomers, reporter molecules, gap regions, RNase activating regions and RNase non-activating regions because all of these components

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were known in the prior art, in various combinations in oligonucleotides for target gene inhibition. One would have been motivated to incorporate sugar, internucleotide and base modifications into oligonucleotides because they were well known in the art to enhance stability, target binding and cellular uptake, as taught previously by Baracchini. One of ordinary skill in the art would have been motivated to do so, so as to optimize for the various prior art oligonucleotide moieties within the chimeric construct for purposes of chimeric stability, enhanced binding abilities. One of ordinary skill in the art would have expected the prior art components to provide for functionalities as taught, irrespective of arrangements of particular components. Furthermore the arrangements of such would have been routine matter of design choice, since all components were well known in the prior art and their successful incorporation into representative stable oligomeric constructs had been demonstrated previously.

Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 6, 7 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arrow et al., Weeks et al and Baracchini et al, the combination in view of the combined teachings of Uhlmann et al. and Heidenreich et al.

The claims are drawn to methods of inhibiting target gene expression in vitro comprising the administration of chimeric oligonucleotides comprising an RNase H activating region and an RNase non-activating region comprising a stretch of contiguous

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unmodified RNA nucleomonomers selected from the groups consisting of adenosine and guanine.

Arrow et al (5,849,902) teach methods of inhibition of target gene expression in vitro comprising the administration of oligonucleotides which target a specific RNA for RNase H degradation, which oligonucleotides contain nuclease resistant bases, including the incorporation of 2'-O-modifications into oligonucleotides for enhancing stability. Arrow teaches an RNase non-activating region within the oligonucleotide and the presence of modified nucleotides within the RNase activating region, as well as modifications within the RNase non-activating region, which oligonucleotides are optimally between 15-50 nucleotides (col. 3-col. 4). Arrow also teaches the significance of the location of the RNase activating region within the antisense construct on the oligonucleotide's stability (col. 8, line 14-col. 9, line 17; tables II and III).

Weeks et al (USPN 5,734,040) teach the incorporation of unmodified purines to enhance stability of antisense constructs (col. 5, lines 32-36). Weeks discloses the use of purine strings to enhance stability of unmodified oligonucleotides over pyrimidines.

Baracchini et al (USPN 5,801,154) teach the inhibition of target gene expression in vitro comprising the administration of oligonucleotides that specifically target a gene of known sequence, which oligonucleotides optionally comprise sugar, base and internucleotide modifications for enhancing target binding, cellular uptake and oligonucleotide stability (col. 6-8).

The primary references do not disclose the specific use of purine ribonucleotides over deoxyribonucleotides.

Uhlmann et al (USPN (Chem. Rev., 90: 544-579, 1990) teach the choice of incorporating ribonucleotides over deoxyribonucleotides in antisense application, wherein the former are less costly (p. 558, section entitled "2'-Modified Oligoribonucleotides").

Heidenreich et al (J. Biol. Chem. 269:213102138, 1994) teach the superior stability of purines to ribonuclease degradation compared to pyrimidines (;. 2131, middle paragraph).

It would have been obvious to one of ordinary skill in the art to utilize modified oligonucleotides which specifically target a target gene of known sequence in vitro because Baracchini taught the routine use of modified oligonucleotides comprising antisense sequences that specifically target a gene of known sequence and inhibit its expression in vitro. It would have obvious to one of ordinary skill in the art to have constructed the oligonucleotides taught by Arrow which contain RNase activating as well as RNase non-activating regions and incorporate unmodified purines in the RNase non-activating region of the chimera because Weeks and Uhlmann both teach advantages of doing such compared to pyrimidine incorporation for enhancing oligonucleotide stability from nuclease digestion. One of ordinary skill would have expected that unmodified purine ribonucleotides (adenosine and guanine) would have provided for enhanced ability for chimeric constructs when placed into the RNase non-activating region because they are less susceptible to nuclease degradation than pyrimidines. One of ordinary skill in the art would have been motivated to construct chimeric oligomers with unmodified adenosine and guanine in the RNase non-activating

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region in order to enhance the construct's stability. One of ordinary skill in the art would have been motivated to incorporate modified internucleotide linkages at various positions in the construct and juxtaposing them in positions with non-modified internucleotide linkages would be a routine matter of design choice.

Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 8-15 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arrow et al., Baracchini et al., Gryaznov et al. and Friesen et al., the combination further in view of Weeks et al., Uhlmann et al. and Heidenreich et al, Troy et al and Bennett et al.

The claimed invention is drawn to methods of inhibiting target gene expression in vitro comprising administration for at least three days of a composition comprising a cationic lipid and a chimeric oligomer, which oligomer comprises an RNase H activating region, an RNase non-activating region, modified internucleoside linkages including P-alkoxyphosphotriester and phosphorothioate linkages, an inverted nucleomonomer, biotin, regions of nucleotide gaps within the chimera which contain modified nucleotides, which optionally occupy different regions of the chimeric construct relative to the 5' and 3' termini and relative to other components within the chimeric construct, and an RNase non-activating region comprising a stretch of contiguous unmodified RNA nucleomonomers selected from the group consisting of adenosine and guanine residues, and which oligonucleotide optionally additionally comprises an affinity

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enhancing agent that is not adjacent to the RNase H activating region, and which oligomer optionally comprises a 3'-blocking group, and an antennepedia transporting peptide.

Arrow et al (5,849,902) teach methods of inhibition of target gene expression in vitro comprising the administration of oligonucleotides which target a specific RNA for RNase H degradation, which oligonucleotides contain nuclease resistant bases, including the incorporation of 2'-O-modifications into oligonucleotides for enhancing stability. Arrow teaches an RNase non-activating region within the oligonucleotide and the presence of modified nucleotides within the RNase activating region, as well as modifications within the RNase non-activating region, which oligonucleotides are optimally between 15-50 nucleotides (col. 3-col. 4).

Baracchini et al (USPN 5,801,154) teach the incorporation of sugar, base and internucleotide modifications into antisense oligonucleotides for enhancing target binding, cellular uptake and oligonucleotide stability, including phosphorothioate phosphorothioate linkages, 2'-alkoxy modification, chimeric oligonucleotides and regions of gapped oligonucleotides within the chimera (col. 6-8).

Gryaznov et al (USPN 5,965,720) teach the use of reporter moieties on oligonucleotides, including biotin for use as a diagnostic tool (col. 4).

Friesen (USPN 5,594,122) teaches the use of compositions containing parallel stranded nucleic acids, including 3'-3' and 5'-5' inversions (e.g., 3' blocked by such an inversion) (col. 3).

The primary references of Arrow et al., Baracchini et al., Gryaznov et al. and Friesen et al do not teach the incorporation of stretches of adenosine or guanine residues into the RNase non-activating region, nor antennepedia transport peptides, nor cationic lipid containing compositions for cellular delivery.

Weeks et al (USPN 5,734,040) teach the incorporation of unmodified purines to enhance stability of antisense constructs (col. 5, lines 32-36). Weeks discloses the use of purine strings to enhance stability of unmodified oligonucleotides over pyrimidines.

Uhlmann et al (USPN (Chem. Rev., 90: 544-579, 1990) teach the choice of incorporating ribonucleotides over deoxyribonucleotides in antisense application, wherein the former are less costly (p. 558, section entitled "2'-Modified Oligoribonucleotides"). Uhlmann also teaches the use of interactive groups in combination with antisense oligonucleotides and categorized these interactive groups as either acting through the complementary DNA or RNA sequences, based on chemical modifications such as photocrosslinkers or artificial endonucleases, or alternatively categorized as oligonucleotides with intercalating residues which cause no change in the target nucleic acid (pages 573-575, section entitle "Antisense oligonucleotides with interactive groups"). Furthermore a relationship between the proximity of such affinity enhancing sites, RNase activation sites and RNase cleavage has been taught by Uhlmann (p. 572, bottom right paragraph through page 573, upper left paragraph).

Heidenreich et al (J. Biol. Chem. 269:213102138, 1994) teach the superior stability of purines to ribonuclease degradation compared to pyrimidines (;. 2131, middle paragraph).

Troy et al (USPN 5,929,042) teach the addition of targeting peptides to oligonucleotides, including antennepedia peptides for purposes of enhancing cellular delivery of oligonucleotides (col. 5).

Bennett et al (Molec. Pharm. 41:1023-1033, 1990) teach the use of cationic lipids in the cellular uptake of oligonucleotides (fig. 3, page 1026).

It would have been obvious to one of ordinary skill in the art to design and construct the chimeric oligonucleotides claimed including the modified internucleotide linkages, sugar modifications, inverted nucleomonomers, reporter molecules, gap regions, RNase activating regions and RNase non-activating regions because all of these components were known in the prior art, in various combinations in oligonucleotides used for target gene inhibition, as taught previously by Arrow et al., Baracchini et al., Gryaznov et al. Friesen et and Uhlmann et al. It would have been obvious to one of ordinary skill in the art to have constructed the oligonucleotides taught by Arrow which contain RNase activating as well as RNase non-activating regions and incorporate unmodified purines in the RNase non-activating region of the chimera because Weeks and Uhlmann both teach advantages of doing such compared to pyrimidine incorporation for enhancing oligonucleotide stability from nuclease digestion. One of ordinary skill would have expected that unmodified purine ribonucleotides (adenosine and guanine) would have provided for enhanced ability for chimeric

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constructs when placed into the RNase non-activating region because they are less susceptible to nuclease degradation than pyrimidines. One of ordinary skill in the art would have been motivated to construct chimeric oligomers with unmodified adenosine and guanine in the RNase non-activating region in order to enhance the construct's stability. Unmodified residues and unmodified internucleotide linkages in such structures are historically considered inherent properties of oligonucleotides.

One of ordinary skill in the art would have been motivated to incorporate modified internucleotide linkages at various positions in the construct and juxtaposing them in positions with non-modified internucleotide linkages would be a routine matter of design choice. And one of ordinary skill in the art would have expected that the incorporation of terminal inversions would block the 3' end of the oligonucleotide and would enhance oligonucleotide stability, as taught previously by Friesen. One of ordinary skill in the art would have been motivated to incorporate or attach a transporting peptide, including the well known antennepedia peptide to enhance appropriate target cell delivery, as taught previously by Troy. One of ordinary skill in the art would have been motivated to administer compositions comprising the modified oligomeric constructs claimed in combination with cationic lipids because transfection techniques routinely used at the time of the instant invention included such lipid compositions, as taught previously by Bennett et al, and such techniques routinely included the incubation of these compositions with target cells from one to three days. One of ordinary skill in the art would have had a reasonable expectation of success in achieving target cellular uptake of these modified oligomers in vitro using the compositions claimed. And one of

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ordinary skill in the art would have expected that the various modifications would provide for a functional RNase activating oligomer with enhanced ability to target an appropriate target cell in vitro and would be more stable than unmodified oligomeric counterparts.

The references collectively considered by one of ordinary skill in the art nevertheless would have suggested the construction of stable and effective chimeric oligonucleotide constructs using all the modifications and features encompassed by the claimed invention.

For these reasons, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765**.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz, can be reached on (571) 272-0763. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
11-25-06

J. Zara
TC 1600
JANE ZARA, PH.D.
PRIMARY EXAMINER